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Concordance for Childhood Cancer in Twins

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The causes of most childhood cancer remain elusive; some children clearly have a genetic predisposition, but in the majority the relative contributions of environmental and host factors are not established. One approach to this question is through twin concordance studies, but only the most common malignancy, acute leukemia, has been studied to date, owing to the rarity of other forms of childhood cancer. The aim of the study was to determine the concordance rates for childhood cancer in twins, in order to clarify the importance of constitutional predisposition for a range of tumor types. Twins with cancer were ascertained through three cooperative clinical trials groups, a cancer-twin registry, and a large pediatric hospital. Subjects were sent a postal questionnaire requesting information on cancer concordance and zygosity. Data were obtained on 556 twins with cancer. Three twin pairs, out of 197 twin pairs (76 monozygous, MZ, twin pairs), were concordant for leukemia, giving an MZ case-wise concordance rate (5%) that is substantially lower than previously reported. The case-wise MZ concordance for non-retinoblastoma solid tumors was 2.2%: Two twin pairs were concordant for CNS tumors, one was concordant for neuroblastoma, and two twin pairs were concordant for cancer but not for the type of cancer. The results of the present study, together with previous data from population studies of siblings and offspring, suggest that there is not in general a strong constitutional genetic component for childhood cancers other than retinoblastoma.

Key words: childhood cancer, twin, concordance

INTRODUCTION

Constitutional genetic factors are known to be important determinants of risk in some children who develop cancer. Of the various types of tumors seen in children, the best understood in this respect is retinoblastoma, which arises from a germline mutation in approximately 40% of cases [1]. The pattern of inheritance in these children is like that of an autosomal dominant gene with 90% penetrance. For other tumor types, the role of genetic factors in determination of a child's risk is less well understood. Observations on the medical and/or family history of a subset of such children suggest that genetic factors are involved. Some cases arise in association with genetic disease including neurofibromatosis, Down syndrome, tuberous sclerosis, Fanconi's anemia, and ataxia telangiectasia. Others occur as part of a familial cancer syndrome which includes soft tissue and bone sarcomas, brain tumors, leukemia in children, and breast cancer in the mother—the Li-Fraumeni syndrome—which is due to a germ-cell mutation of the p53 gene [2]. It is reasonable to assume that there are additional cases of heritable cancer that are not part of any recognized familial cluster. Wilms' tumor is bilateral in 7% of cases, multicentric in another 10%, and arises in conjunction with developmental abnormalities such as nephroblast-omatosis, organomegaly, genito-urinary abnormalities, aniridia, and mental retardation in approximately 13% of cases, suggesting the presence of a constitutional defect with multiple manifestations [3]. However, it is notable that familial Wilms' cases do not appear to have an increase in bilaterality or associated congenital abnormalities. Finally, the failure of investigators to reproducibly and convincingly identify environmental exposures that might explain more than a small fraction of the observed cases provides indirect support for the existence of constitutional determinants of childhood cancers.

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TABLE I. Eligible Twin Pairs and the Number of Questionnaires Returned (With Reasons for Non-Response), by Source of Twins

	NWTS	CCG	SJCRH	ITS	UKCCSG	Total
Indentified	45	262	67	509	98	
Ineligible	0	7	0	60	12	
Eligible	45	255	67	449	84	
Duplicate ascertainment[a]	0	7	0	44	0	
Non-duplicate eligibles	45	248	67	405	84	849
No current address	10	90	15	4	15	134
Questionnaire not returned	1	10	1	117	10	139
Parent refused	0	6	5	6	3	20
Returned	34	142	43	278	54	556

[a]Twins ascertained via two sources that have been excluded to avoid double-counting. The No. in each column excludes those already counted as eligible to the left of that column.

On the other hand, there are data to indicate that most childhood cancers (excluding bilateral retinoblastoma) are not primarily due to an inherent genetic susceptibility. Studies of cancer in siblings of children with cancer provide relative risk estimates that are only slightly elevated: For example, for siblings of children with leukemia, the estimated relative risk is 2.3 for leukemia and 1.3 for other cancers [4,5]. Long-term follow-up of cancer survivors has shown an increased risk of second malignancy, but in many instances this can be attributed to the effects of therapy. The children of cancer survivors appear to have little if any increased risk of cancer [6–9], other than for retinoblastoma survivors.

One approach to the study of genetic susceptibility to disease is to determine disease concordance in twins, comparing genetically identical monozygous (MZ) twins with dizygous (DZ) twins who are genetically equivalent to siblings. Owing to the rarity of childhood cancers, few studies of this sort have been attempted, and the data for cancers other than leukemia are very limited. This paper describes concordance data on twins ascertained through a major pediatric oncology center, a collaborative group of pediatric oncologists, a cancer-twin registry, and two cooperative clinical trial groups.

MATERIALS AND METHODS

Case Ascertainment

The five contributors to this study were The International Twin Study (ITS), the U.S. Childrens Cancer Group (CCG), the U.K. Children's Cancer Study Group (UKCCSG), St. Jude Children's Research Hospital (SJCRH), and the National Wilms' Tumor Study (NWTS). The ITS, based at the University of Southern California, is a registry for twins with at least one member affected with cancer (or a select group of other diseases). CCG and NWTS are cooperative clinical trials groups based in the United States and Canada. The UKCCSG is a collaborative group comprising most of the specialist pediatric oncologists in the United Kingdom and the Republic of Ireland. SJCRH is a private nonprofit research center for cancer and other selected catastrophic diseases of childhood.

Each of the collaborating centers had a different means of ascertaining cases. ITS routinely places advertisements in newspapers in the United States for twins with cancer. Those responding to the notices are interviewed by telephone to elicit basic registration information; medical records are then gathered for disease confirmation and classification. CCG and NWTS included a question regarding twin status on their standard case registration forms; these forms were usually completed by data managers at the treating institution. NWTS also obtained twin status from a questionnaire completed by patient families. The UKCCSG registers all cases treated by its members, and the registration form includes a question on twin status. SJCRH medical records department routinely codes twin status of all newly diagnosed patients. Data from the UKCCSG was limited to twins aged 0–14 years at diagnosis; for the other sources, the age range was 0–20 years. Patients included in this study were registered between 1972 and 1989 (CCG), 1971 and 1985 (NWTS), 1977 and 1986 (UKCCSG), and 1964 and 1987 (SJCRH); the ITS does not draw cases from a defined population.

Data Collection

The parents of the twins were sent a brief questionnaire that requested information on zygosity and the diagnosis of cancer and congenital abnormalities in the co-twin and other siblings of the case. For some older twins registered through the ITS, the questionnaire was completed by the co-twin. Return rates by source are given in Table I.

Zygosity was asked about directly and was also determined through questions on gender, shared placenta and/or fetal membranes, similarity of appearance, and blood tests if any. Comparison of the categorization made by the parent and that based on an algorithm that combined more specific observations showed close agree-

TABLE II. Comparison of Zygosity Stated by the Parent and Zygosity Determination Based on an Algorithm Combining Data in the Questionnaire Relating to Zygosity

Parent report of zygosity	Unlike sex	Zygosity determined by algorithm		
		DZ	Uncertain	MZ
DZ	129	108	58	30
Uncertain	—	3	5	11
MZ	—	3	26	183

ment (Table II). The zygosity score was calculated for like-sexed twins as follows: a point was added to the score when (a) the twins were described as "alike as two peas in a pod," (b) either the twin's parents or siblings "sometimes" mistook the twins for each other, (c) friends, relatives, teachers, or other associates (two or more of these groups) "often" mistook the twins, (d) the twins had the same placenta and fetal membranes, or (e) monozygosity was said to be determined by blood test. A point was subtracted if (a) the twins were "not alike" (note: since "of ordinary family likeness" was available as an alternative response, this choice suggests the twins were of quite different appearance), (b) friends, relatives, teachers, or other associates never mistook the twins, or dizygosity was said to be established by blood test. Twins scoring greater than 1 were categorized as MZ, those below 0 were considered DZ, and values of 0 and 1 were of uncertain zygosity. For the purposes of this analysis, twins were considered to be DZ if either the parent categorization of the algorithm designated them so and the other categorization did not disagree (N = 298), similarly for MZ (N = 220), and to be of uncertain zygosity only if the two categorizations disagreed (N = 33) or both placed the twins in the uncertain group (N = 5).

Cancer in the co-twin was based on the information supplied by the respondent and, for sources other than the ITS, was not verified through solicitation of medical records.

Concordance Estimation

Twin concordance can be expressed as a case-wise concordance ratio which estimates the probability that the co-twin of an affected twin is also affected. If there are C concordant pairs, of which x were doubly ascertained (that is, both affected twins were probands), and D discordant pairs in the series, the case-wise concordance is $(C + x)/(C + x + D)$ [10].

RESULTS

Of the 556 twin pairs for whom questionnaires were returned, the interval between diagnosis of the proband and completion of the questionnaire was 5 years or more for 93% of twin pairs and at least 10 years for 75% of twins. The number of twin pairs, by diagnosis, is given in Table III, with the number reported to be concordant (at the same site) given in parentheses. Overall, 12 twin pairs were concordant for cancer of the same type, and an additional two pairs were concordant for cancer of different types. Two concordant pairs were doubly ascertained.

Details of the tumors reported for the concordant twins are given in Table IV. The twin pair (No. 4) with acute lymphocytic leukemia in one twin, "lymphoma and leukemia" in the other, and uncertain zygosity requires comment, since the general quality of responses in this questionnaire cast doubt on the accuracy of the data. Attempts were made to recontact the parents of this case for confirmation, without success. The twin pair (No. 7) with glioma and optic nerve tumor also had neurofibromatosis. The similarity of ages at diagnosis in concordant twins is worth noting.

The casewise MZ concordance rate for leukemia in this study is 5% (three concordant, one of which was doubly ascertained, out of 76 MZ pairs), and the overall (MZ plus DZ) case-wise concordance is 2.5%. Restricting consideration to those under age 6 years, MZ concordance is 9.5%. Case-wise concordance for all other cancers combined (including pair 8 from Table IV, but excluding all retinoblastomas) is 1.2% overall, and 2.2% in MZ twins. In these calculations, twin pair 4 (Table IV) was counted as concordant for leukemia.

There were three additional twin pairs known to be concordant for leukemia (at 2, 20, and 23 months of age) that were excluded because the families could not be contacted. These were all CCG cases, diagnosed in 1974, 1977, and 1977, respectively, and the time since diagnosis, combined with the possibility that both twins may have died, could explain the failure to make contact with their parents. We can calculate the concordance rate, with these cases included, if we assume that the proportion of these twins that were MZ and had leukemia was the same as for those who returned the questionnaires and if we assume that no other concordant cases would have been found in this group. With these assumptions, the case-wise MZ concordance for leukemia would be 10%.

DISCUSSION

A key issue is whether there are biases with respect to twin concordance, and in view of the low concordance we report, whether systematic under-reporting of concordant twins occurred for any of the data sources. For the ITS twins the extent of possible bias cannot be easily determined since the ITS is dependent on voluntary self-registration. Commonly the person making contact is one of the twins so that there could be under ascertainment of concordant twin pairs in which both have died. For twins from the other sources, it is possible to estimate the completeness of ascertainment, since the patient popula-

TABLE III. Number of Twin Pairs by Diagnosis and Zygosity*

	N	Zygosity		
		DZ	MZ	Uncertain
Acute lymphocytic leukemia	167	90	63 (2)	14[a]
Acute myelogenous leukemia	30	14	13 (1)	3
Hodgkins lymphoma	31	15	13	3
Non-Hodgkins lymphoma	18	14	3	1
Lymphoma (NOS)	11	7	4	0
Medulloblastoma	16	8	8	0
Other CNS tumors	51	30	16 (2)	5
Neuroblastoma	33	20	11 (1)	2
Retinoblastoma	18	10 (2)	7 (4)	1
Wilms' tumor	60	29[b]	27	4
Liver tumor	10	2	8	0
Osteosarcoma	16	9	4	3
Ewing's sarcoma	21	10	10	1
Bone tumor (NOS)	10	7	3	0
Soft tissue sarcoma	46	20	25	1
Ovarian/testis	4	3	1	0
Histiocytosis X	7	4	3	0
All sites	549	292 (2)	219 (10)	38

*The No. concordant for cancer (at the same site) are shown in parentheses. Seven twins excluded from this table had no diagnosis recorded (two cases) or cancer at a rare site (five cases).
[a]One case with "lymphoma and leukemia" in the twin.
[b]One case with acute lymphocytic leukemia in the twin.

TABLE IV. Details of All Twin Pairs Concordant for Cancer*

No.	Source	Zygosity	Sex	Diagnosis	Age	Diagnosis	Age
1	CCG	MZ	F/F	Acute lymphocytic leukemia	13 m	Acute lymphocytic leukemia	13 m
2	ITS	MZ	F/F	Acute lymphocytic leukemia	3 y	Acute lymphocytic leukemia	3 y
3	ITS	MZ	F/F	Acute monocytic leukemia	2 y	Acute monocytic leukemia	2 y
4	CCG	Unk	M/M	Acute lymphocytic leukemia	5 y	Lymphomas and leukemia (NOS)	—
5	ITS	MZ	F/F	Glioblastoma	16 y	Glioblastoma	23 y
6	CCG	MZ	M/M	Neuroblastoma	4 m	Neuroblastoma	4 m
7	UKCCSG	MZ	F/F	Mixed glioma	5 y	Optic nerve tumor	5 y
8	ITS	DZ	F/F	Wilms' tumor	3 y	Acute lymphocytic leukemia	3 y
9	ITS	MZ	F/F	Retinoblastoma (unilateral)	4 m	Retinoblastoma (bilateral)	4 m
10	ITS	MZ	F/F	Retinoblastoma (bilateral)	10 m	Retinoblastoma (bilateral)	10 m
11	CCG	DZ	M/M	Retinoblastoma (bilateral)	10 m	Retinoblastoma (bilateral)	10 m
12	CCG	DZ	M/F	Retinoblastoma (bilateral)	4 m	Retinoblastoma (bilateral)	4 m
13	ITS	MZ	M/M	Retinoblastoma	5 m	Retinoblastoma	6 m
14	ITS	MZ	M/M	Retinoblastoma	3 m	Retinoblastoma	3 m
						& Osteosarcoma	—

*Both twins in pairs 1 and 14 were ascertained as probands.

tion from which they were taken is known. About one pregnancy in 80 is a twin pregnancy and, allowing for higher perinatal mortality in twins, approximately 2% of the population are twins. In this study, the percentages of all children with cancer that were identified as twins were 0.9% (CCG), 1.0% (UKCCSG), 1.2% (SJCRH), and 1.4% (NWTS). Thus there appears to be under ascertainment, to a varying extent, that reflects the fact that the information on twin status was of no immediate value at the time that it was collected and was perhaps not recorded assiduously nor checked for accuracy. This is likely to have been a particular problem when the information was recorded by a person not in direct contact with the patient or family. Under ascertainment raises the possibility of selection biases, but it seems likely that any bias would be in favor of concordance, since twin status is more likely to be known and accurately recorded for twins concordant for cancer. Another possible explanation for the deficit of twins is that, as Stewart suggested [17], there are some unrecognized fetal deaths among concordant twin pairs and, when one affected child dies in this way, the surviving twin is recorded as a singleton with cancer.

Biases may also arise from differential response to the questionnaire mailing (Table I). Many of the non-responses were due to the lack of a current address, and a

TABLE V. Published Series of Twins With Childhood Leukemia, Showing Concordant Pairs*

	Zygosity					Concordant pairs				
						Twin 1		Twin 2		
Reference	N	DZ	MZ	Date	Zyg	Age	Dx	Age	Dx	Sex
MacMahon and Levy [11]	72	50	22[a]	(1954)	MZ	11 m	ALL	15 m	ALL	F/F
				(1959)	MZ	3 y	AL	4 y	ALL	M/M
				(1958)	MZ	5 m	ALL	5 m	ALL	F/F
				(1960)	MZ	4 y	AML	4 y	AML	M/M
				(1952)	MZ	7 y	AL	9 y	AS	F/F
Jackson et al. [12]	48	40	8[a]	(1962)	MZ	(6 y)	AL	(6 y)	ALL	M/M
				(1952)	MZ	(8 y)	ALL	(10 y)	AS	F/F
Miller [13]	245	163	82[b]	(1960–7)	ZU	(3 m)	AL	(4 m)	AL	M/M
				(1960–7)	ZU	(2 y)	L	(2 y)	AL	M/M
				(1960–7)	ZU	(4 y)	AL	(5 y)	AL	F/F
				(1960–7)	ZU	(5 y)	AL	(5 y)	ALL	M/M
				(1960–7)	ZU	(3 y)	AL	(6 y)	AL	F/F
				(1960–7)	ZU	(9 m)	AML	(9 m)	AML	M/M
				(1960–7)	ZU	(7 m)	AML	(14 m)	AML	M/M
Fraumeni et al. [14]	28	85	10	(1971)	MZ	(2 m)	AMoL	(3 m)	AMoL	M/M
Iverson [16]	11	6	5[a]				⟨None⟩			
Inskip et al. [15]	31	20	11[a]	1947	ZU	2 y	ALL	4 y	ALL	F/F
				1954	ZU	11 m	ALL	16 m	ALL	F/F
Draper et al. [4]			40				⟨None⟩			

*Where possible, the date of diagnosis for the first twin is given; otherwise, the date of the death is listed (in parentheses). Age given is at diagnosis, or at death (values in parentheses). ZU refers to unknown zygosity. The patient that died in 1952, reported by MacMahon and Levy [11], was also included in the report of Jackson et al. [12]

ALL, acute lymphocytic leukemia; AL, acute leukemia; AML, acute myeloblastic leukemia; AS, acute stem cell leukemia; L, leukemia; AMoL, acute monoblastic leukemia.

[a]No. of MZ twins in these series estimated using Weinberg's method.

[b]Proportion of twins that are MZ estimated to be 0.33.

bias toward discordance would only be expected if the concordant pairs were more likely to be untraced. The number of definite parental refusals was small, but many of the non-returns will have been due to parents deciding not to participate or not being motivated to respond. It seems reasonable that parents of concordant twins would have been more likely to respond to the mailed questionnaire, producing an over-estimation of the concordance rates.

Last, we did not attempt to validate the cancers in the co-twins. The effect of doing so, if any, would have been to re-classify some concordant twins as discordant. Once again, although this is a potential source of bias it does not affect our primary conclusion which is that concordance rates for most tumors were very low. Follow-up from the date of diagnosis was at least 10 years in 75% of cases. Some co-twins who did not have cancer at the date of contact could develop it at a later date, perhaps at the same site as the index twin. For tumor types with a defined childhood age peak the co-twin will, in many instances, have reached an age at which the risk is slight. Other co-twins will be near adulthood (or soon to reach age 21), at which point they could no longer become concordant for *childhood* cancer. Thus although the possibility exists that additional concordant twin pairs would be ascertained with longer follow-up, age-of-onset corrections would have a minimal effect on the estimated concordances.

Many of the published reports of twins with childhood cancer are single case reports which are likely to be highly selective; for this reason, we reviewed only those articles presenting results of systematic collection of cancer in twins. Table V summarizes the data for acute leukemia concordance in twins. One notable feature of these data is the relatively young age at diagnosis (or death) for many of these doubly affected twin pairs. The median age for those listed in Table V is 2 years, which can be compared to a median age at diagnosis of ALL equal to 56 months for all children registered with CCG. This observation might suggest a genetic predisposition for childhood leukemia but is also compatible with the hypothesis that the leukemia in one of the twins is a consequence of in utero cross-transfusion of malignant cells from the twin originally affected. Support for the hypothesis that both leukemias arise from a single transformed cell can be found in the reports of Chaganti et al. [18] and Ford et al. [19] who showed identical non-constitutive chromosomal changes in leukemic cells from MZ twins concordant for acute lymphocytic leukemia. The possibility remains that a shared genetic risk is re-

sponsible for some concordant acute leukemias, particularly when the disease does not manifest until several years after birth.

In some studies, zygosity was not known and the number of MZ pairs, necessary for calculation of MZ concordance rate, was calculated from the numbers of like- and unlike-sex pairs using the method of Weinberg [20] which is based on the assumption that the number of like- and unlike-sexed DZ twins will be approximately equal. Although the zygosity of the concordant twins was not known in two of the studies, the fact that all nine pairs, in Table V, with unknown zygosity were the same sex suggests that most and perhaps all were MZ twins.

For all but one of the acute leukemia series listed in Table V, the concordant pairs were doubly ascertained, since no method of secondary ascertainment (that is, follow up of co-twins to determine their disease status) was used to find affected co-twins of probands; the exception is the series reported by MacMahon and Levy [11], in which one concordant pair appeared to be singly ascertained (with the affected co-twin ascertained through interview). Summing across all studies, using Weinberg's method where necessary to estimate the number of MZ pairs and assuming the concordant twins were all MZ, the case-wise concordance for childhood leukemia in MZ twins is 17%.

The data for solid tumors are less complete, largely because of the difficulty of obtaining twin series with such rare diseases. A single concordant pair (with leukemia and a brain tumor) was observed in 59 twin pairs in a recent study of childhood cancer in twins [21]. Olson et al. [22] found one pair of DZ twins concordant for Wilms' tumor in a series of 71 twins with Wilms' tumor. Draper et al. [4] reported four concordant like-sexed twin pairs, with oligodendroglioma, multiple meningiomas, Wilms' tumor, and retinoblastoma, respectively, in a series which included the majority of cases of cancer occurring below age 15 in Britain over a period of about 20 years.

The epidemiological observations discussed earlier, in support of a constitutional genetic basis for some childhood cancers, and the recent exciting developments in the understanding of the molecular genetic basis of these cancers has served to focus attention on genetic factors in childhood cancer. However, it is important not to lose sight of the fact that patients for whom a constitutional genetic abnormality can be demonstrated, or presumed, represent only a small fraction of all cases. As was pointed out in the Introduction, studies on risks to first degree relatives of children with cancer indicate that familial risks are generally small. At the same time, a major role for environmental factors has yet to be established, despite considerable efforts over several decades.

In data from this study there were no concordant pairs in 282 dizygous twins with malignancies other than retinoblastoma, except for one pair that developed cancers at different sites. One case in a co-twin can be compared to an expected number of approximately 0.5, based on a cumulative risk of childhood cancer to age 15 of one in 600 in the population as a whole. Since the risk for siblings of childhood cancer patients (in the absence of known genetic disease) is approximately twice that for the general population [4], it is clear that there is no evidence from this study that the dizygous co-twin of an affected child is at greater risk than any other sibling. A higher concordance rate would have pointed to shared environmental factors (presumably more similar for twins than for siblings), since dizygotic twins are genetically equivalent to siblings.

The number of malignancies in monozygous co-twins does exceed expectations (six non-retinoblastomas observed; less than one expected). Of these, however, three were leukemias diagnosed at the same age (13 months, 2 and 3 years, respectively), and one may suspect that they are examples of transfer of malignant cells in utero. While the remaining three concordant twin pairs (out of 136 non-retinoblastoma, non-leukemia cases) exceed the expected number for siblings of cancer cases (less than one), it is remarkable that so few monozygous twins of children with cancer develop the same cancer.

It is possible to estimate from our data the maximum percent of childhood solid tumors (other than retinoblastoma) that might be due to germline mutation with high penetrance. Assuming a Poisson distribution for the number of observed concordances (N = 3) from 136 MZ twins, the upper 95% confidence bound for the Poisson mean is 8.77, from which we can determine that the probable upper limit on the proportion with a highly penetrant mutation common to both twins is 6.4%. An equivalent estimate for leukemia would have little meaning, since both germline and somatic mutations can manifest as a twin concordance. These results confirm the view that, while the study of heritable genetic factors predisposing to childhood cancers may advance our understanding of the molecular genetic basis of both the familial and sporadic forms of these cancers, the overall heritable genetic contribution to childhood cancer risk is small.

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